Delineating the early transcriptional specification of the mammalian trachea and esophagus.

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Public Summary:
The genome-scale transcriptional programs that specify the mammalian trachea and esophagus are unknown. Though NKX2-1 and SOX2 are hypothesized to be co-repressive master regulators of tracheoesophageal fates, this is untested at a whole transcriptomic scale and their downstream networks remain unidentified. By combining single-cell RNA-sequencing with bulk RNA-sequencing of Nkx2-1 mutants and NKX2-1 ChIP-sequencing in mouse embryos, we delineate the NKX2-1 transcriptional program in tracheoesophageal specification, and discover that the majority of the tracheal and esophageal transcriptome is NKX2-1 independent. To decouple the NKX2-1 transcriptional program from regulation by SOX2, we interrogate the expression of newly-identified tracheal and esophageal markers in Sox2/Nkx2-1 compound mutants. Finally, we discover that NKX2-1 binds directly to Shh and Wnt7b and regulates their expression to control mesenchymal specification to cartilage and smooth muscle, coupling epithelial identity with mesenchymal specification. These findings create a new framework for understanding early tracheoesophageal fate specification at the genome-wide level.

Scientific Abstract:
The genome-scale transcriptional programs that specify the mammalian trachea and esophagus are unknown. Though NKX2-1 and SOX2 are hypothesized to be co-repressive master regulators of tracheoesophageal fates, this is untested at a whole transcriptomic scale and their downstream networks remain unidentified. By combining single-cell RNA-sequencing with bulk RNA-sequencing of Nkx2-1 mutants and NKX2-1 ChIP-sequencing in mouse embryos, we delineate the NKX2-1 transcriptional program in tracheoesophageal specification, and discover that the majority of the tracheal and esophageal transcriptome is NKX2-1 independent. To decouple the NKX2-1 transcriptional program from regulation by SOX2, we interrogate the expression of newly-identified tracheal and esophageal markers in Sox2/Nkx2-1 compound mutants. Finally, we discover that NKX2-1 binds directly to Shh and Wnt7b and regulates their expression to control mesenchymal specification to cartilage and smooth muscle, coupling epithelial identity with mesenchymal specification. These findings create a new framework for understanding early tracheoesophageal fate specification at the genome-wide level.